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DOCUMENT-IDENTIFIER: US 6146841 A

TITLE: Methods for identifying compounds that bind to CSAPK-3 molecules and fragments thereof

Abstract Text (1):

The present invention provides methods for identifying compounds that bind to CSAPK-3, a cardiovascular system associated protein kinase.

Brief Summary Text (2):

Phosphate tightly associated with protein has been known since the late nineteenth century. Since then, a variety of covalent linkages of phosphate to proteins have been found. The most common involve esterification of phosphate to serine, threonine, and tyrosine with smaller amounts being linked to lysine, arginine, histidine, aspartic acid, glutamic acid, and cysteine. The occurrence of phosphorylated proteins implies the existence of one or more protein kinases capable of phosphorylating amino acid residues on proteins, and also of protein phosphatases capable of hydrolyzing phosphorylated amino acid residues on proteins.

Brief Summary Text (3):

Protein kinases play critical roles in the regulation of biochemical and morphological changes associated with cellular growth and division (D'Urso, G. et al. (1990) Science 250: 786-791; Birchmeier, C. et al. (1993) Bioessays 15: 185-189). They serve as growth factor receptors and signal transducers and have been implicated in cellular transformation and malignancy (Hunter, T. et al. (1992) Cell 70: 375-387; Posada, J. et al. (1992) Mol. Biol. Cell 3: 583-592; Hunter, T. et al. (1994) Cell 79: 573-582). For example, protein kinases have been shown to participate in the transmission of signals from growth-factor receptors (Sturgill, T. W. et al. (1988) Nature 344: 715-718; Gomez, N. et al. (1991) Nature 353: 170-173), control of entry of cells into mitosis (Nurse, P. (1990) Nature 344: 503-508; Maller, J. L. (1991) Curr. Opin. Cell Biol. 3: 269-275) and regulation of actin bundling (Husain-Chishti, A. et al. (1988) Nature 334: 718-721). Protein kinases can be divided into two main groups based on either amino acid sequence similarity or specificity for either serine/threonine or tyrosine residues. A small number of dual-specificity kinases are structurally like the serine/threonine-specific group. Within the broad classification, kinases can be further sub-divided into families whose members share a higher degree of catalytic domain amino acid sequence identity and also have similar biochemical properties. Most protein kinase family members also share structural features outside the kinase domain that reflect their particular cellular roles. These include regulatory domains that control kinase activity or interaction with other proteins (Hanks, S. K. et al. (1988) Science 241: 42-52).

Brief Summary Text (5):

The present invention is based, at least in part, on the discovery of novel nucleic acid molecules and proteins encoded by such nucleic acid molecules, referred to herein as "Cardiovascular System Associated Protein Kinase" ("CSAPK") proteins. The CSAPK nucleic acid and protein molecules of the present invention are useful as modulating agents in regulating a variety of cellular processes, e.g., cardiac cellular processes. Accordingly, in one aspect, this invention provides isolated nucleic acid molecules encoding CSAPK proteins or biologically active portions thereof, as well as nucleic acid fragments suitable as primers or hybridization probes for the detection of CSAPK-encoding nucleic acids.

Brief Summary Text (18):

Another aspect of this invention features isolated or recombinant CSAPK proteins and polypeptides. In one embodiment, the isolated protein, preferably a CSAPK-1 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site. In another embodiment, the isolated protein, preferably a CSAPK-1 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and has an amino acid sequence which is at least 51%, 55%, 60%, 65%, 70%, 75%, 80%, 81%, 85%, 90%, 95%, 99% or more homologous to an amino acid sequence including SEQ ID NO:2. In yet another embodiment, the isolated protein, preferably a CSAPK-1 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is expressed and/or functions in cells of the cardiovascular system. In an even further embodiment, the isolated protein, preferably a CSAPK-1 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and plays a role in signalling pathways associated with cellular growth, e.g., signalling pathways associated with cell cycle regulation. In another

embodiment, the isolated protein, preferably a CSAPK-1 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3.

Brief Summary Text (19):

In another embodiment, the isolated protein, preferably a CSAPK-2 protein, includes at least one dual specificity kinase catalytic domain and at least one ATP-binding site. In another embodiment, the isolated protein, preferably a CSAPK-2 protein, includes at least one dual specificity kinase catalytic domain, at least one leucine zipper-basic region, and at least one ATP-binding site. In another embodiment, the isolated protein, preferably a CSAPK-2 protein, includes at least one dual specificity kinase catalytic domain and at least one ATP-binding site and has an amino acid sequence which is at least 42%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more homologous to an amino acid sequence including SEQ ID NO:5. In yet another embodiment, the isolated protein, preferably a CSAPK-2 protein, includes at least one dual specificity kinase catalytic domain, and at least one ATP-binding site and is expressed and/or functions in cells of the cardiovascular system. In an even further embodiment, the isolated protein, preferably a CSAPK-2 protein, includes at least one dual specificity kinase catalytic domain, and at least one ATP-binding site and plays a role in signalling pathways associated with cellular growth, e.g., signalling pathways associated with cell cycle regulation. In another embodiment, the isolated protein, preferably a CSAPK-2 protein, includes at least one dual specificity kinase catalytic domain, and at least one ATP-binding site and is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:4 or SEQ ID NO:6.

Brief Summary Text (20):

In yet another embodiment, the isolated protein, preferably a CSAPK-3 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site. In another embodiment, the isolated protein, preferably a CSAPK-3 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and has an amino acid sequence which is at least 41%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more homologous to an amino acid sequence including SEQ ID NO:8. In yet another embodiment, the isolated protein, preferably a CSAPK-3 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is expressed and/or functions in cells of the cardiovascular system. In an even further embodiment, the isolated protein, preferably a CSAPK-3 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and plays a role in signalling pathways associated with cellular growth, e.g., signalling pathways associated with cell cycle regulation. In another embodiment, the isolated protein, preferably a CSAPK-3 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:7 or SEQ ID NO:9.

Brief Summary Text (21):

In another embodiment, the isolated protein, preferably a CSAPK-4 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site. In another embodiment, the isolated protein, preferably a CSAPK-4 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and has an amino acid sequence which is at least 59%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more homologous to an amino acid sequence including SEQ ID NO:11. In yet another embodiment, the isolated protein, preferably a CSAPK-4 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is expressed and/or functions in cells of the cardiovascular system. In an even further embodiment, the isolated protein, preferably a CSAPK-4 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and plays a role in signalling pathways associated with cellular growth, e.g., signalling pathways associated with cell cycle regulation. In another embodiment, the isolated protein, preferably a CSAPK-4 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:10 or SEQ ID NO:12.

Brief Summary Text (22):

In another embodiment, the isolated protein, preferably a human CSAPK-5 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site. In yet another embodiment, the isolated protein, preferably a human CSAPK-5 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and has an amino acid sequence which is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more homologous to an amino acid sequence including SEQ ID NO:14. In yet another embodiment, the isolated protein, preferably a human CSAPK-5 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is expressed and/or functions in cells of the cardiovascular system. In an even further embodiment, the isolated protein, preferably a human CSAPK-5 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and plays a role in signalling pathways associated with cellular growth, e.g., signalling pathways associated with cell cycle regulation. In another embodiment, the isolated protein, preferably a human CSAPK-5 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is able to interact with Nck (described in Lehman et al. (1990) Nucleic Acids Res. 18:1048). In another embodiment, the isolated protein, preferably a human CSAPK-5 protein, includes at least one Ser/Thr kinase domain, and at least one ATP-binding site and is encoded by a nucleic acid molecule

having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:13 or SEQ ID NO:15.

Detailed Description Text (2):

The present invention is based, at least in part, on the discovery of novel molecules, referred to herein as "Cardiovascular System Associated Protein Kinase" or "CSAPK" nucleic acid and polypeptide molecules, which play a role in or function in signalling pathways associated with cellular growth. In one embodiment, the CSAPK molecules modulate the activity of one or more proteins involved in cellular growth or differentiation, e.g., cardiac cell growth or differentiation. In another embodiment, the CSAPK molecules of the present invention are capable of modulating the phosphorylation state of a CSAPK molecule or one or more proteins involved in cellular growth or differentiation, e.g., cardiac cell growth or differentiation.

Detailed Description Text (3):

In a preferred embodiment, the CSAPK molecules are protein kinases which are expressed and/or function in cells of the cardiovascular system, e.g., cells of the heart, the blood vessels, and/or the blood.

Detailed Description Text (4):

As used herein, the term "protein kinase" includes a protein or polypeptide which is capable of modulating its own phosphorylation state or the phosphorylation state of another protein or polypeptide. Protein kinases can have a specificity for (i.e., a specificity to phosphorylate) serine/threonine residues, tyrosine residues, or both serine/threonine and tyrosine residues, e.g., the dual specificity kinases. As referred to herein, protein kinases preferably include a catalytic domain of about 200-400 amino acid residues in length, preferably about 200-300 amino acid residues in length, or more preferably about 250-300 amino acid residues in length, which includes preferably 5-20, more preferably 5-15, or preferably 11 highly conserved motifs or subdomains separated by sequences of amino acids with reduced or minimal conservation. Specificity of a protein kinase for phosphorylation of either tyrosine or serine/threonine can be predicted by the sequence of two of the subdomains (VIb and VIII) in which different residues are conserved in each class (as described in, for example, Hanks et al. (1988) Science 241:42-52) the contents of which are incorporated herein by reference). These subdomains are also described in further detail herein.

Detailed Description Text (5):

Protein kinases play a role in signalling pathways associated with cellular growth. For example, protein kinases are involved in the regulation of signal transmission from cellular receptors, e.g., growth-factor receptors; entry of cells into mitosis; and the regulation of cytoskeleton function, e.g., actin bundling. Thus, the CSAPK molecules of the present invention may be involved in: 1) the regulation of transmission of signals from cellular receptors, e.g., cardiac cell growth factor receptors; 2) the modulation of the entry of cells, e.g., cardiac precursor cells, into mitosis; 3) the modulation of cellular differentiation; 4) the modulation of cell death; and 5) the regulation of cytoskeleton function, e.g., actin bundling.

Detailed Description Text (6):

Inhibition or over stimulation of the activity of protein kinases involved in signaling pathways associated with cellular growth can lead to perturbed cellular growth, which can in turn lead to cellular growth related disorders. As used herein, a "cellular growth related disorder" includes a disorder, disease, or condition characterized by a deregulation, e.g., an upregulation or a downregulation, of cellular growth. Cellular growth deregulation may be due to a deregulation of cellular proliferation, cell cycle progression, cellular differentiation and/or cellular hypertrophy. Examples of cellular growth related disorders include cardiovascular disorders such as heart failure, hypertension, atrial fibrillation, dilated cardiomyopathy, idiopathic cardiomyopathy, or angina; proliferative disorders or differentiative disorders such as cancer, e.g., melanoma, prostate cancer, cervical cancer, breast cancer, colon cancer, or sarcoma.

Detailed Description Text (10):

In one embodiment, the isolated proteins of the present invention, preferably CSAPK-1 proteins, are identified based on the presence of at least one "Ser/Thr kinase site" and at least one "ATP-binding region." As used herein, the term "Ser/Thr kinase site" includes an amino acid sequence of about 200-400 amino acid residues in length, preferably 200-300 amino acid residues in length, and more preferably 250-300 amino acid residues in length, which is conserved in kinases which phosphorylate serine and threonine residues and found in the catalytic domain of Ser/Thr kinases. Preferably, the Ser/Thr kinase site includes the following amino acid consensus sequence X.sub.9-g -X-G-X.sub.4 -V-X.sub.12 -K-X-.sub.(10-19) -E-X.sub.66 -h-X.sub.8 -h-r-D-X-K-X.sub.2 -N-X.sub.17 -K-X.sub.2 -D-f-g-X.sub.21 -p-X.sub.13 -w-X.sub.3-g -X.sub.55 -R-X.sub.14 -h-X.sub.3 (SEQ ID NO:17) (where invariant residues are indicated by upper case letters and nearly invariant residues are indicated by lower case letters). The nearly invariant residues are usually found in most Ser/Thr kinase sites, but can be replaced by other amino acids which, preferably, have similar characteristics. For example, a nearly invariant hydrophobic amino acid in the above amino acid consensus sequence would most likely be replaced by another hydrophobic amino acid. Ser/Thr kinase domains are described in, for example, Levin D. E. et al. (1990) Proc. Natl. Acad. Sci. USA 87:8272-76, the contents of which are incorporated herein by reference.

Detailed Description Text (14):

Accordingly, another embodiment of the invention features isolated CSAPK-1 proteins and polypeptides having a CSAPK-1 activity. Preferred proteins are CSAPK-1 proteins having at least one Ser/Thr kinase site and at least one ATP-binding region and, preferably, a CSAPK-1 activity. Additional preferred proteins have at least one Ser/Thr kinase site and at least one ATP-binding region and are, preferably, encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3.

Detailed Description Text (18):

In another embodiment, the isolated proteins of the present invention, preferably CSAPK-2 proteins, are identified based on the presence of at least one dual specificity kinase catalytic domain and at least one ATP-binding region. In yet a further embodiment, the isolated proteins of the present invention, preferably CSAPK-2 proteins, are identified based on the presence of at least one dual specificity kinase catalytic domain, at least one ATP-binding region, and at least one leucine zipper region.

Detailed Description Text (19):

As used herein, the term "dual specificity kinase catalytic domain" includes an amino acid sequence of 200-400 amino acid residues in length, preferably 200-300 amino acid residues in length, and more preferably 250-300 amino acid residues in length, which includes a kinase catalytic domain whose primary sequence is a hybrid between a serine/threonine kinase catalytic domain and a tyrosine kinase catalytic domain. Kinases containing the dual specificity kinase catalytic domain are capable of phosphorylating both serine/threonine and tyrosine residues. Preferably, a dual specificity kinase catalytic domain includes the following amino acid consensus sequence X.sub.9 -G-X-G-X.sub.2 -G-X-V-X.sub.12 -K-X-.sub.(10-19) -E-X.sub.34 -G-X.sub.40 -H-R-D-X-K-X.sub.2 -N-X.sub.17 -K-X.sub.2 -D-F-G-X.sub.19 -W-X-A-P-E-X.sub.13 -W-X.sub.7 -E-X.sub.6 -P-X.sub.36 -C-W-X.sub.6 -R-P-X-F-X.sub.14 (SEQ ID NO:19). Dual specificity kinase catalytic domains are described in, for example, Holzman L. B. et al. (1994) J Biol. Chem. 269:30808-817, the contents of which are incorporated herein by reference. Amino acid residues 31-277 of the CSAPK-2 protein comprise a dual specificity kinase catalytic domain.

Detailed Description Text (23):

Accordingly, another embodiment of the invention features isolated CSAPK-2 proteins and polypeptides having a CSAPK-2 activity. Preferred proteins are CSAPK-2 proteins having at least one dual specificity kinase catalytic domain and at least one ATP-binding region. Yet further preferred CSAPK-2 proteins have at least one dual specificity kinase catalytic domain, at least one ATP-binding region, and at least one leucine zipper region. Preferred proteins have at least one dual specificity kinase catalytic domain, at least one ATP-binding region and, preferably, a CSAPK-2 activity. Additional preferred proteins have at least one dual specificity kinase catalytic domain, at least one ATP-binding region and are, preferably, encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:4 or SEQ ID NO:6.

Detailed Description Text (27):

In another embodiment, the isolated proteins of the present invention, preferably CSAPK-3 proteins, are identified based on the presence of at least one Ser/Thr kinase site and at least one ATP-binding region. The Ser/Thr kinase site and the ATP-binding region are described herein. Amino acid residues 5-164 of the CSAPK-3 protein comprise a Ser/Thr kinase domain.

Detailed Description Text (30):

Accordingly, another embodiment of the invention features isolated CSAPK-3 proteins and polypeptides having a CSAPK-3 activity. Preferred proteins are CSAPK-3 proteins having at least one Ser/Thr kinase site and at least one ATP-binding region. Additional preferred proteins have at least one Ser/Thr kinase site, at least one ATP-binding region, and, preferably a CSAPK-3 activity. Additional preferred proteins have at least one Ser/Thr kinase site and at least one ATP-binding region and are, preferably, encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:7 or SEQ ID NO:9.

Detailed Description Text (34):

In another embodiment, the isolated proteins of the present invention, preferably CSAPK-4 proteins, are identified based on the presence of at least one Ser/Thr kinase site and at least one ATP-binding region. The Ser/Thr kinase site and the ATP-binding region are described herein. Amino acid residues 11 to 75 of the CSAPK-4 protein comprise a Ser/Thr kinase domain.

Detailed Description Text (37):

Accordingly, another embodiment of the invention features isolated CSAPK-4 proteins and polypeptides having a CSAPK-4 activity. Preferred proteins are CSAPK-4 proteins having at least one Ser/Thr kinase site and at least one ATP-binding region. Additional preferred proteins have at least one Ser/Thr kinase site, at least one ATP-binding region, and, preferably a CSAPK-4 activity. Additional preferred proteins have at least one Ser/Thr kinase site and at least one ATP-binding region and are, preferably, encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:10 or SEQ ID NO:12.

Detailed Description Text (41):

In another embodiment, the isolated proteins of the present invention, preferably CSAPK-5 proteins, are identified based on the presence of at least one Ser/Thr kinase site and at least one ATP-binding region. In yet another embodiment, the isolated proteins of the present invention, preferably CSAPK-5 proteins, are identified based on the presence of at least one Ser/Thr kinase site, and at least one ATP-binding region.

Detailed Description Text (44):

Accordingly, another embodiment of the invention features isolated CSAPK-5 proteins and polypeptides having a CSAPK-5 activity. Preferred proteins are CSAPK-5 proteins having at least one Ser/Thr kinase site and at least one ATP-binding region. Additional preferred proteins have at least one Ser/Thr kinase site, at least one ATP-binding region, and, preferably a CSAPK-5 activity. Additional preferred proteins have at least one Ser/Thr kinase site and at least one ATP-binding region and are, preferably, encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:13 or SEQ ID NO:15.

Detailed Description Text (157):

The ability of the CSAPK protein to phosphorylate a CSAPK target molecule can be determined by, for example, an in vitro kinase assay. Briefly, a CSAPK target molecule, e.g., an immunoprecipitated CSAPK target molecule from a cell line expressing such a molecule, can be incubated with the CSAPK protein and radioactive ATP, e.g., [γ -³²P] ATP, in a buffer containing MgCl₂ and MnCl₂, e.g., 10 mM MgCl₂ and 5 mM MnCl₂. Following the incubation, the immunoprecipitated CSAPK target molecule can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, e.g., a PVDF membrane, and autoradiographed. The appearance of detectable bands on the autoradiograph indicates that the CSAPK substrate has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the CSAPK substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards.

Detailed Description Text (244):

The invention is based, at least in part, on the discovery of five human genes encoding members of the CSAPK family. The human CSAPK family members were isolated from cDNA libraries which were prepared from tissue obtained from subjects suffering from congestive heart failure of ischemic and idiopathic origin. Briefly, a cardiac tissue sample was obtained from a biopsy of a patient suffering from congestive heart failure. MRNA was isolated from the cardiac tissue and a cDNA library was prepared therefrom using art known methods (described in, for example, Molecular Cloning A Laboratory Manual, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press: 1989). Positive clones were isolated following comparison to homologs in public protein databases, including a comparison with known kinases and/or examination of the sequence for protein motifs of kinases.

Detailed Description Text (251):

A BLASTN 1.4.9 search, using a score of 100 and a word length of 12 (Altschul et al. (1990) J Mol. Biol. 215:403) of the nucleotide sequence of human CSAPK-1 revealed that CSAPK-1 is similar to the human protein kinase HPK-1 coding sequence (Accession No. V23831). This nucleic acid molecule is approximately 70% identical to CSAPK-1, over nucleotides 388-1214.

Detailed Description Text (252):

CSAPK-2 is similar to the human MST mRNA for serine/threonine kinase (Accession No. Z48615). This nucleic acid molecule is approximately 54% identical to CSAPK-2, over nucleotides 482-805.

Other Reference Publication (2):

Deiss, L.P. et al., "Identification of a Novel Serine/Threonine Kinase and a Novel 15-kd protein as Potential Mediators of the Gamma Interferon-Induced Cell death," Genes Dev. vol. 9 No. 1 15-30 (1995).

Other Reference Publication (3):

Dorow, D.S. et al., "Identification of a New Family of Human Epithelial Protein Kinases Containing Two Leucine/isoleucine-Zipper Domains," Eur. J. Biochem. vol. 213 No. 2. 701-710 (1993).

Other Reference Publication (5):

Katoh, M. et al., "Cloning and Characterization of MST, a Novel (Putative) Serine/Threonine Kinase with SH3 Domain," Oncogene vol 10, No. 7, 1447-1451 (1995).

Other Reference Publication (6):

Kawai, T. et al., "Zip-Kinase, a Novel Serine/Threonine Kinase which Mediates Apoptosis," Mol. Cell. Biol. vol. 18, 1642-1651 (1998).

Other Reference Publication (8):

Schultz, S.J. et al., "Identification of 21 Novel Human Protein Kinases, Including 3 Members of a Family Related to the Cell Cycle Regulator nimA of *Aspergillus Nidulans*," Cell Growth Differ. vol, 4, No. 10, 821-830 (1993).

Other Reference Publication (9):

Schultz, S.J. et al., "Cell Cycle-Dependant Expression of Nek2, a Novel Human Protein Kinase Related to the NIMA Mitotic Regulator of *Aspergillus Nidulans*," Cell Growth Differ. vol, 5, No. 6, 625-635 (1994).

Other Reference Publication (10):

Su, Y.C. et al., NIK is a New ste20-Related Kinase That Binds NCK and MEKK1 and activates the SAPK/JNK cascade via a Conserved Regulatory Domain.

CLAIMS:

1. A method for identifying a compound which modulates the binding or kinase activity of a polypeptide comprising the amino acid sequence of SEQ ID NO:8, the method comprising:

a) contacting a cell expressing the polypeptide with a test compound under conditions suitable for modulation of the binding or kinase activity of the polypeptide; and

b) detecting modulation of the binding or kinase activity of the polypeptide by the test compound.

2. A method for identifying a compound which modulates the binding or kinase activity of a polypeptide consisting of the amino acid sequence of SEQ ID NO:8; the method comprising:

a) contacting a cell expressing the polypeptide with a test compound under conditions suitable for modulation of the binding or kinase activity of the polypeptide; and

b) detecting modulation of the activity of the binding or kinase polypeptide by the test compound.

3. A method for identifying a compound which modulates the binding or kinase activity of a naturally occurring allelic variant of a polypeptide consisting of the amino acid sequence of SEQ ID NO:8, wherein the allelic variant is encoded by a nucleic acid molecule which hybridizes to the complement of a nucleic acid molecule consisting of SEQ ID NO:7 or 9, in 6.times.SSC at 45.degree. C., followed by one or more washes in 0.2.times.SSC, 0.1% SDS at 50-65.degree. C., the method comprising:

a) contacting a cell expressing the allelic variant with a test compound under conditions suitable for modulation of the binding or kinase activity of the allelic variant; and

b) detecting modulation of the binding or kinase activity of the allelic variant by the test compound.

4. A method for identifying a compound which modulates the kinase activity of a polypeptide comprising at least 100 contiguous amino acids of SEQ ID NO:8, the method comprising:

a) contacting a cell expressing the polypeptide with a test compound under conditions suitable for modulation of the kinase activity of the polypeptide; and

b) detecting modulation of the kinase activity of the polypeptide by the test compound.

10. A method for identifying a compound which modulates the binding or kinase activity of a polypeptide comprising the amino acid sequence of SEQ ID NO:8, the method comprising:

a) contacting the polypeptide with a test compound under conditions suitable for modulation of the binding or kinase activity of the polypeptide; and

b) detecting modulation of the binding or kinase activity of the polypeptide by the test compound.

11. A method for identifying a compound which modulates the binding or Kinase activity of a polypeptide consisting of the amino acid sequence of SEQ ID NO:8, the method comprising:

a) contacting the polypeptide with a test compound under conditions suitable for modulation of the activity of the binding or

kinase polypeptide; and

b) detecting modulation of the activity of the binding or Kinase polypeptide by the test compound.

12. A method for identifying a compound which modulates the binding or kinase activity of a naturally occurring allelic variant of a polypeptide consisting of the amino acid sequence of SEQ ID NO:8, wherein the allelic variant is encoded by a nucleic acid molecule which hybridizes to the complement of a nucleic acid molecule consisting of SEQ ID NO:7 or 9, in 6.times.SSC at 45.degree. C., followed by one or more washes in 0.2.times.SSC, 0.1% SDS at 50-65.degree. C., the method comprising:

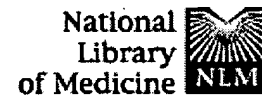
a) contacting the allelic variant with a test compound under conditions suitable for modulation of the binding or kinase activity of the polypeptide; and

b) detecting modulation of the activity of the binding or kinase allelic variant by the test compound.

13. A method for identifying a compound which modulates the kinase activity of a polypeptide comprising at least 100 contiguous amino acids of SEQ ID NO:8, the method comprising:

a) contacting the polypeptide with a test compound under conditions suitable for modulation of the kinase activity of the polypeptide; and

b) detecting modulation of the kinase activity of the polypeptide by the test compound.



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☐ 1: Cell Death Differ 1998 May;5(5):346-56

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p75NTR: A study in contrasts.

Barker PA.

Center for Neuronal Survival, Montreal Neurological Institute, McGill University, 3801 University Avenue, Montreal, Quebec, Canada H3A 2B4. mdpb@musica.mcgill.ca

The p75 neurotrophin receptor (p75NTR) and trkA, trkB and trkC mediate the physiological effects of the neurotrophins. The trk receptors are responsible for the stereotypical survival and growth properties of the neurotrophins but defining the physiological function of the p75NTR has proven difficult. The p75NTR binds each of the neurotrophins with low nanomolar affinity whereas the three trk receptors show strong binding preferences for individual neurotrophins; in some cell types, p75NTR is the only neurotrophin receptor whereas in others it is co-expressed with the trks. The analysis of p75NTR function has been complicated by the fact that the predominant physiological role of p75NTR changes dramatically depending on cell context. Available data suggests that in cells where p75NTR is co-expressed with trk receptors, p75NTR functionally collaborates with the trks to either enhance responses to preferred trk ligands, to reduce neurotrophin-mediated trk receptor activation resulting from non-preferred ligands or to facilitate apoptosis resulting from neurotrophin withdrawal. In cells lacking trk expression, p75NTR can act autonomously to activate ligand-dependent signaling cascades that may in some circumstances result in apoptosis but probably not through pathways utilized by its apoptotic brethren in the TNF receptor superfamily. Potential mechanisms for each of these functions of p75NTR are

considered and the physiological implications of this unique signaling system are discussed.

Publication Types:

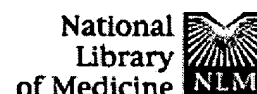
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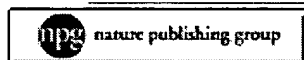
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Miller FD, Kaplan DR.

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